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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,455	02/21/2002	James C. Paulson	019957-011212US	3039

20350 7590 06/15/2005

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,455	PAULSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,62,64,66,68 and 81-83* is/are pending in the application.

4a) Of the above claim(s) *62,64 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,66 and 81-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

GOD

DETAILED ACTION

Claims 60, 62, 64, 66, 68, 81-83 are now pending in this application. Claims 60, 66, 81-83 are now under consideration, Claims 62, 64, 68 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on , have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Examiner acknowledges the request to transfer sequence data from parent application. Amendments to first line of the specification is also acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60, 81-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of sialylating a saccharide group on a recombinant glycoprotein using the specific sialyltransferase (ST), α 2,3-ST isolated specifically from *C.jejuni*, does not reasonably provide enablement for such a method wherein any α2,3-ST isolated from any bacteria including variants, mutants and recombinants are used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 60, 81-83 are so broad as to encompass the use of any bacterial α2,3-ST including variants, mutants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the use of extremely large number of α2,3-ST enzymes broadly encompassed in the claimed method. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to few bacterial ST, one of which is α 2,3-ST from *C.jejuni*. It would require undue experimentation of the skilled artisan to use any α2,3-ST including variants, mutants and recombinants, from any source or to make and use such polypeptides in the claimed method. The specification is limited to teaching the use of the α 2,3-ST from *C.jejuni* but provides no guidance with regard to the making of variants and mutants of the same. In view of the great breadth of the claim, amount of experimentation required to make/use the polypeptides in the claimed method, the lack of guidance, working examples of variants, and

unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of any or all bacterial α2,3-STs including variants, mutants and recombinants, because the specification does not establish: (A) a single universal method of isolation of any bacterial α2,3-ST and a single universal method of using such α2,3-ST to sialylate a glycopeptide; (B)regions of the protein structure (i.e., any bacterial α 2,3-ST) which may be modified without affecting its activity; (C) the general tolerance of bacterial α2,3-STs to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue on the bacterial α2,3-ST polypeptide with an expectation of obtaining the desired biological function;

and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all bacterial α2,3-STs with an enormous number of amino acid modifications for use in the claimed method. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of bacterial α2,3-ST having the desired biological characteristics for the claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the above rejection, applicants submit that the disclosure adequately teaches how to use bacterial sialyltransferases to sialylate a recombinant glycoprotein and that even if some bacterial sialyltransferase activities are not able

to sialylate a recombinant glycoprotein, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. Applicants also argue that one of skill would know how to avoid inoperative embodiments and sialylate recombinant glycoproteins using the claimed methods with bacterial sialyltransferase activities without undue experimentation and that the present application provides guidance in the form of assays and working examples for sialylation of recombinant glycoproteins using bacterial sialyltransferase activities. Applicants also assert that only a few bacterial species make sialylated oligosaccharides and are known to provide sialyltransferase activity. Applicants appear to argue

that since there are limited number of bacterial species any experimentation would not be undue. Examiner respectfully disagrees with such an argument. While it can be agreed that there may be limited number of bacterial enzymes as of now new ones may be discovered. Applicants' claims read on method of sialylating substrates encompassing enzymes that have not yet been discovered. Furthermore, irrespective of that fact, claims encompass a method of sialylating substrates using any variants, mutants and recombinants of known bacterial enzymes. However, applicants have not taught those skilled in the art as to how to make those variants or mutants of the known bacterial enzymes. As stated earlier applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because any experimentation to practice the method would not be undue. This is not persuasive because, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known, the skilled artisan producing variants still requires or be provided with guidance for the selection of which specific amino acids in the bacterial polypeptide sequence can be modified and which of the infinite number of variants that result from such modification have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) a single universal method of isolation of any bacterial α2,3-ST and a single universal method of using such α2,3-ST to sialylate a glycopeptide; (B)regions

of the protein structure (i.e., any bacterial α 2,3-ST) which may be modified without affecting its activity; (C) the general tolerance of bacterial α2,3-STs to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue on the bacterial α2,3-ST polypeptide with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence the rejection is maintained.

Claims 60, 81-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 60, 81-83 are directed to a method of using any or all bacterial ST polypeptides including variants, mutants and recombinants. Claims 60, 81-83 are rejected under this section of 35 USC 112 because the claims are directed to the method of use of a genus of polypeptides isolated from bacteria including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue and fragments of the same that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the function of the polypeptide has been provided by applicants which would indicate that they had possession of the genus of polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences, including fragments and variants within the scope of the genus. The genus of polypeptides claimed is a large variable genus

including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the genus for use in the claimed method. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing the specification describes methods of sialylating using recombinant glycoproteins and that they were the first to disclose the use of bacterial sialyltransferases to sialylate glycoproteins. Applicants correctly conclude that the rejection focus is only on the description of the enzymes for use in the claimed method and not the steps of the method. Applicants argue that once bacterial STs were discovered, those skilled in the art would have recognized their use and would not restrict themselves to a particular bacterial enzyme and that the inventors were in possession of the claimed invention. Examiner respectfully disagrees with such an argument. Those skilled in the art would recognize that applicants were in possession of the enzyme isolated from *C.jejuni* but not all or any bacterial α 2,3-ST, including variants and mutants of any bacterial α 2,3-ST since they have not described such variants or provided guidance to make such variants and mutants.

Applicants argue that the invention provides ample disclosure of the steps required to sialylate a recombinant protein and that the steps are straightforward. Examiner agrees with the applicants that the specification describes the methods and the steps used. However, the disclosure does not describe all the bacterial enzymes that can be used in the method. Without the enzymes those skilled in the art would be unable to use such a method.

Lastly, applicants argue that the fact pattern in the instant case is similar or identical to Example 18 of the Written Description Guidelines which analyzes a claim directed to a method of producing a protein of interest in *Neurospora* mitochondria by transforming the nucleic acid that encodes the proteins of interest. Examiner respectfully disagrees that the fact pattern of the instant application is similar or identical to that of Example 18. This is because the claimed method in the Example 18 is drawn to a method wherein any particular nucleic acid sequence encoding a protein of interest is not essential to the claimed invention. However, in the instant case, it cannot be concluded that any bacterial enzyme is not essential to the invention. While the method and its steps may be generic, the enzyme used is highly specific and is essential for the invention. Therefore, unless the genus of the enzyme is described in the specification, those skilled in the art cannot conclude that applicants were in possession of the claimed invention which encompasses the use of any bacterial α 2,3-ST. As discussed in the written description guidelines, the written description requirement for a claimed genus (in this case, the enzymes to be used in the method) may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed method includes the use of species which are widely variant in structure. The genus is structurally diverse as it encompasses polypeptides with α 2,3-ST activity from all or any bacteria including variants, mutants and recombinants. As such, the sole disclosure of functional features present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 60, 66, 81-83 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73, 80-81 of U.S. Patent No. 6,399,336. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 60, 66, 81-83 of the instant application and claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73, 80-81 of the reference patent are both directed to method of sialylating a glycoprotein using bacterial STs, specifically *C.jejuni* α 2,3-ST. The method of sialylation claimed in the instant application and in the reference patent a good number of limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited method includes several embodiments that would anticipate the method claimed in claims 60, 66, 81-83 herein. Claims 60, 66, 81-83 of the instant application listed above cannot be considered patentably distinct over claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73, 80-81 of the reference patent when there is specifically recited embodiment that would anticipate mainly claims 60, 66, 81-83 of the instant application. Alternatively, claims 60, 66, 81-83 cannot be considered patentably distinct over claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73,

80-81 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73, 80-81 of that patent and falls within the scope of claims 60, 66, 81-83 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73, 80-81 of the reference by selecting a specifically disclosed embodiment that supports those claims. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-3, 12, 19-20, 23, 28-29, 32, 45, 50-51, 59-61, 73, 80-81 of the reference patent.

Claims 60, 81-82 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, of co-pending application 10/081,456. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 60, 81-82 of the instant application and claims 1-3 of the reference application are both directed to method of sialylating a glycoprotein using STs. While the method claimed in the instant application is limited to bacterial recombinant ST it would encompass the method of use of recombinant ST3Gal1. The method of sialylation claimed in the instant application and in the reference application, a good number of limitations

are identical to one another. The portion of the specification (and the claims) in the reference application that supports the recited method includes several embodiments that would anticipate the method claimed in claims 60, 81-82 herein. Claims 60, 81-82 of the instant application listed above cannot be considered patentably distinct over claims 1-3, of the reference application when there is specifically recited embodiment that would anticipate mainly claims 60, 81-82 of the instant application. Alternatively, claims 60, 81-82 cannot be considered patentably distinct over claims 1-3, of the reference application when there is specifically disclosed embodiment in the reference that supports claims 1-3, of that application and falls within the scope of claims 60, 81-82 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-3, of the reference by selecting a specifically disclosed embodiment that supports those claims. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-3, of the reference.

In response to the above rejection, applicants have indicated that they will file a T.D once outstanding rejections are resolved. However, Examiner maintains the rejection for reasons of record.

Conclusion

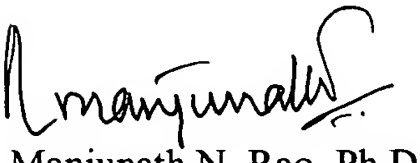
None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

June 2, 2005